National Organization for Women

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Division of Dockets Management (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville, MD 20852

Docket Number 2004D-0002 "New Draft Guidance Document for Breast Implants"

Dear Sir or Madam:

The National Organization for Women (NOW) sponsored a scientific forum in May of 2003 to address the unanswered safety questions related to silicone breast implants. A dozen researchers participated from public and private institutes and universities as well as government health officials from the Armed Forces Institute of Pathology, the National Institutes of Health, and the Food and Drug Administration (FDA). We held the forum out of a conviction that government reliance on industry-supplied data may result in rulings that are beneficial to industry at the cost of consumer health. This objective forum allowed researchers and physicians to identify the outstanding questions of safety and to make recommendations that might serve to improve the study, design and safety of silicone breast implants in the future.

NOW was encouraged by the FDA's decision in January of 2004 to deny the approval of silicone breast implants until additional safety information could be obtained. When the General and Plastic Surgery Advisory Panel met last October, there was a great deal of discussion about the shortcomings of the clinical trials. Because the sponsor was unable to address many aspects of long-term safety, a number of the advisory panel members offered their own recommendations for the trials in order to glean more meaningful information.

While encouraged by the FDA's ultimate decision on Inamed Corporation's silicone breast implant products, it is critical that the agency demand more scientific-based clinical trials from the device manufacturers. Each year, over two hundred thousand women receive breast implants in the United States. Despite the opportunity to evaluate basic safety questions related to silicone breast implants, the current manufacturers have conducted only a few years of surveillance as part of their premarket approval (PMA) applications. We need more information from long-term clinical trials.

The following are our recommendations based on the NOW scientific forum and the advisory panel discussion in October of 2003:

2004D-0002 C6

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Summary of Recommendations

(1) The length of the clinical trials should be increased to address issues of long-term safety prior to approval;
(2) Clinical trials should include a more in-depth evaluation of the mode and clinical consequence of rupture (failure);
(3) If women undergo re-operation with implantation of new devices, the time clock for, at least, a ten year follow-up should be reset;
(4) The Magnetic Resonance Imaging (MRI) cohort should be expanded to include all patients in the clinical trial. In order to obtain an accurate assessment of the risk of silent (asymptomatic) rupture, MRI evaluations should continue throughout the lifetime of the device;
(5) Clinical trials must evaluate any differences between the augmentation and reconstruction cohorts;
(6) Clinical trials must evaluate women in childbearing years and collect information on pregnancy, delivery and breastfeeding complications;
(7) Clinical trials should follow children born to mothers with silicone breast implants to evaluate health or developmental problems;
(8) Follow-up evaluations should include laboratory tests to determine the health risks associated with short- and long-term exposure to silicone gel, specifically rheumatological tests and indicators of chronic inflammation;
(9) Clinical trials must continue to follow women after explantation, even when new silicone breast implants are not implanted.

Details of Recommendations

The length of the clinical trials should be increased to address issues of long-term safety prior to approval. The new draft guidance stipulates that clinical trials collect a minimum of 10 years of prospective patient follow-up. However, it does not specify the amount of follow-up necessary prior to approval to make an accurate assessment of safety. NOW urges the FDA to insist on a full understanding of the long-term risks of device failure (rupture, asymptomatic rupture and gel leakage) and the clinical consequences of failure over the lifetime of the device before they are allowed back on the market. If breast implant devices are intended to remain in a woman's body for 10 to 15 years or longer, clinical trials should be conducted for an appropriate period of time to ascertain the safety over the lifetime of the device.

The idea of preventive explantation was discussed by the advisory panel to reduce the risk of exposure to silicone gel. If it is decided that elective explantation prior to rupture is a recommendation that should be standard, we must have a clear understanding of the time frame in which the majority of failures occur.

Clinical trials need to collect more long-term data *prior* to approval in order to more fully examine the increasing risk of rupture and other complications. Inamed Corporation's data demonstrated significant increases in rupture, silent rupture, CTD signs and symptoms, local complications and re-operations in just a few years of patient follow-up.

FDA advisory panel member Dr. Stephen Li stressed the importance of routine surveillance (in person follow-up) beyond 10 years which should evaluate:

- Rupture over time (intra- and extracapsular);
- Repeat surgeries required by the patients; and,
- Impacts on women during childbearing years and children of women with silicone breast implants.

Dr. Barbara Manno, also on the FDA advisory panel, recommended evaluating the handedness in women with ruptured implants to determine if there is a connection between the dominant hands (e.g. right handed) and implant rupture. Dr. Li also recommended evaluating the effect of implant volume on rupture, since volumes can vary by a factor of 4 (anywhere from 90 to 100 up to 750 milliliters).

Clinical trials should include a more in-depth evaluation of the mode and clinical consequence of rupture (failure). Understanding why and when implants fail is critically important if we are to make an assessment of the long-term risks of these devices. Further, as Dr. Michael Choti, an FDA advisory panel member pointed out, understanding failure is critical if we are ever to make improvements on the devices.

If women undergo re-operation with implantation of new devices, the time clock for 10 year follow-up should be reset. Inamed's data demonstrated high re-operation rates, including re-operation with the implantation of new breast implant devices. Since there are numerous "styles" of silicone breast implants on the market it is important that women are followed for a minimum of 10 years from the implantation of each new device.

The MRI cohort should be expanded to include all patients in the clinical trial. In order to obtain an accurate assessment of the risk of silent (asymptomatic) rupture, MRI evaluations should be continued throughout the lifetime of the device. The prevalence and risk of silent (asymptomatic) rupture remain unknown. MRI evaluations will help in the evaluation of device failure and the presence of silicone gel migration into surrounding breast tissue. The data collected from the MRI study should be cross-referenced with laboratory and clinical evaluations to make an assessment of the short- and long-term risks of exposure to silicone gel.

Clinical trials must evaluate any differences between the augmentation and reconstruction cohorts. Inamed Corporation's short-term clinical data revealed significantly higher rates of complications (including rupture) and re-operations for the reconstruction cohort. We need to understand this trend before the devices are allowed back on the market. Breast cancer survivors should have a clear understanding of the risks of these devices, particularly if their risks far exceed that of the general population undergoing augmentation.

Clinical trials must evaluate women in childbearing years and collect information on pregnancy, delivery and breastfeeding complications. If a woman experiences a breastfeeding complication she should be evaluated by MRI to determine the nature of the

complication, including any evidence of rupture or gel migration. Samples of breast milk should be taken at appropriate intervals while the mother is breast feeding.

Clinical trials should follow children born to mothers with silicone breast implants to evaluate health or developmental problems. Second-generation effects are particularly important if there is a diagnosed rupture and subsequent gel migration. FDA advisory panel member Dr. Ruth Lawrence, Professor of Pediatric, Obstetrics and Gynecology at the University of Rochester, recommended in the presence and absence of rupture and gel migration we recommend at a minimum:

- An evaluation of the potential exposure levels during pregnancy;
- Collecting blood cords because exposure is considered greater transplacentally than through breast milk; and,
- Following children born to mothers with silicone breast implants for a minimum of 10 years.

Follow-up evaluations should include laboratory tests to determine the health risks associated with short- and long-term exposure to silicone gel, specifically rheumatological tests and indicators of chronic inflammation. There has been an ongoing discussion around the long-term systemic effects of silicone gel exposure. At the NOW forum in May of 2003, researchers concurred that there is little information in this area. We do not understand the health implications of silicone gel exposure nor do we have an understanding of dose-response.

Considering that there are a series of laboratory tests that can shed light on health complications prior to and at intervals post implantation, we recommend the following tests at a minimum:

- Anti-nuclear antibodies (full screen)
- Markers for inflammation such as Erythrocyte Sedimentation Rate (ESR) and C-Reactive Proteins (CRP)
- Total immunoglobulin levels
- Screen for monoclonal gammapathies
- Combined blood counts (CBC)
- Natural Killer cell counts
- Rheumatoid factors
- Anti-polymer antibodies

A baseline should be conducted prior to implantation, and routine laboratory tests should be conducted at annual follow-up examinations.

Clinical trials must continue to follow women after explantation, even when new silicone breast implants are not implanted. In the presence of silicone gel migration, women will continue to be exposed to components of the silicone gel-filled breast implants. The retrieval study is critical in determining whether silicone gel has migrated into capsular tissue. Since the implications for long-term exposure of silicone gel are

unknown, clinical trials must follow women who have had explantation of silicone breast implants even if new implants were not elected. These women should receive routine follow-up examinations by physicians as well as the series of laboratory tests mentioned above.

The manufacturers have had decades to evaluate the risks of these devices and to make improvements to the design and function of silicone breast implants. At the advisory panel meeting in October of 2003, Inamed Corporation announced that the device under review was essentially the very same device that had been on the market since the 1980s. The FDA must demand that clinical trials are conducted in a manner that fully examines the short- and long-term risks of these devices prior to approval.

There is no substitute for prospective clinical trials and the FDA must recognize that post-approval conditions and registries are of little value to women making a decision on silicone breast implants after approval. We need clinical data that demonstrate the long-term safety of these devices before they are allowed back on the market in an unrestricted capacity. Furthermore, clinical trials that evaluate modes of failure and long-term risks are our only mechanism for improving the devices. Annual reports from the manufacturers to the FDA are an appropriate and necessary tool to ensure clinical trials are progressing pursuant to FDA requirements and to monitor the health of the women involved in clinical trials.

We also strongly recommend that the FDA collaborate with the National Institutes of Health (National Institute of Environmental Health Sciences and National Cancer Institute) as well as the Armed Forces Institute of Pathology to develop clinical trials designed to address our advancing knowledge of the risks associated with these devices. Research being conducted at these agencies may help to elucidate the long-term risks associated with silicone breast implants as well as identify or develop safer breast implant products.

Women have the right to make informed choices about safe devices. It is FDA's responsibility to ensure that that right is not diminished by limited, poorly constructed and implemented clinical trials.

Sincerely,

Kim Gandy
President

Thank you for considering these comments.